## REMARKS

Following entry of the above amendment, claims 13-36, 38, and 42-48 will be pending in the application, claims 44-53 having been newly added. No claims are newly canceled. Claims 13, 18, 21, 27, 29-36, 38, 42, and 43 are amended above. Support for new claims 44-48 can be found in the specification at, e.g., page 7, lines 21-22; page 8, lines 1-2, 10-11, and 19-20; and page 6, lines 19-21. Support for new claims 49-53 can be found in the claims as originally filed and throughout the specification, e.g., at page 2, line 18, to page 4, line 23; page 6, lines 19-21; page 8, lines 24-29, and page 9, lines 3-7. Support for the remaining amendments is discussed in detail below. No new matter has been added.

The Office action mailed December 4, 2007 (the "Office Action") follows the decision by the Board of Patent Appeals and Interferences rendered on August 28, 2007 (the "Board Decision"), in which the Board overruled the rejection for lack of enablement, declined to rule on the obviousness rejections, and instructed the Examiner to reopen prosecution in order to consider certain additional questions regarding written description, claim interpretation, and statutory subject matter. The Board invited Appellant to "take an active role in clarifying the foregoing issues." Board Decision at page 11. In an effort to engage in a dialog with the Examiner to address the remaining issues in accordance with the Board's invitation, Appellant's representatives participated in a telephonic interview with the Examiner on October 18, 2007 (the "Interview"). During the Interview, Appellants pointed out where in the specification one could find indirect support for the claim terms in question: (1) "instructing a patient to inhale", and (2) "instructing a patient to inhale the composition on demand." The details of this Interview are summarized in the interview summary filed by Appellant on November 13, 2007 (and re-transmitted on November 21, 2007). It was Appellant's understanding that, at the end of the Interview, the Examiner agreed that the claims on file were supported by adequate written description. It therefore came as a surprise to receive a new Office action in which the Examiner took the opposite position, for reasons that were not raised by the Examiner during the Interview. The grounds for rejection raised in the Office Action are discussed below.

**35 USC § 112, paragraph 1, written description**

All of the pending claims were newly rejected for lack of written description. The Office Action alleges that the terms "instructing a patient to inhale" and "instructing a patient to inhale the composition on demand" lack adequate support in the specification as originally filed. This is despite the fact that these terms were added to the claims by amendments filed in 2001, so have been in the claims throughout several years of prosecution. A question regarding whether these terms have adequate written description was raised by the Examiner in an Office action mailed March 21, 2003. The issue was overcome in the response filed June 19, 2003, followed shortly thereafter by a Notice of Allowance mailed July 9, 2003.[1] In issuing the Notice of Allowance, the Examiner implicitly indicated her agreement that claims containing the very same terms now at issue possessed adequate written description. If the Examiner does not have access to those papers from the file, Appellant can supply them. For the Examiner's convenience, the relevant text on page 7 of the response filed June 19, 2003, is reproduced here:

> The Examiner has rejected claims 13, 35, 36 and 42 under 35 U.S.C. 112, first paragraph. The Examiner states that "the term 'on demand' in claims 13, 35 and 36, and the phrase 'instructed to take a maintenance dose of the composition... to inhale additional doses' in claim 42 lack literal support."
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> While these phrases may lack literal, word-for-word support in the specification, it is axiomatic that the patent statute does not require such *ipsis verbis* support. See, e.g., Fujikawa v. Wattanasin, 39 USPQ2d 1895 (Fed. Cir. 1996). The Federal Circuit has confirmed that "the test for determining compliance with the written description requirement of §112 is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later clamed subject matter, rather than the presence or absence of literal support in the specification for the claim language." In re Kaslow, 217 USPQ 1089 (Fed. Cir. 1983.)
>
> In this case, the artisan would understand that the inventor had possession at the time filing of the claimed "on demand" administration, for example based on the teaching of "as needed use (Pro Re Nata, PRN)" at p. 4, lines 12-15 of Applicant's specification and in Example 6. The claim language of claim 42 finds support, for example, in Example 5, in which a patient is instructed to use the claimed combination for maintenance therapy, and then to take additional doses on an as needed basis.

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[1] This application would have issued long ago if Appellants had not filed a Request for Continued Examination with an information disclosure statement at that point, to satisfy their duty of disclosure.

By allowing the claims after this response (following an additional amendment requested by the Examiner, which additional amendment did not affect the terms at issue), the Examiner implicitly acknowledged that the terms "instructing the patient" and "on demand" were adequately supported in the specification as filed. It is therefore puzzling why she believes the facts are any different now than in 2003. In particular, it is puzzling why she believes that "instructing a patient" "may be a next step" (see Office Action at page 5) following administration of the composition. Instructing a patient would necessarily occur prior to the patient's self-administering the composition, and not as a "next step." That a patient would have to be instructed in how often to use the inhaler (e.g., twice a day for maintenance treatment, or alternatively on an as-needed basis when symptoms arise) is implicit Appellant's specification. One of ordinary skill in the art of treating asthma patients would understand that this is implicit. It is therefore unclear why the Examiner (a) believes it is not implicit in the specification, and (b) would constitute a "next step" after the administration has taken place. Clarification of this point is respectfully requested, as it may reflect a fundamental misunderstanding of the nature of the invention that could potentially make progress difficult.

In an effort to remove this written description issue once and for all, Appellant has amended the claims to remove the terms "**instructing the patient to inhale**" (and the like) and "**on demand,**" even though the specification clearly communicated both of those concepts to a reader of ordinary skill in the art of treating asthma patients. Claim 13 as presently amended reads as follows:

> 13. (Currently amended) A method of prevention and treatment of a patient's asthma symptoms, the method comprising
>
> (i) providing an inhaler to the patient, the inhaler containing a composition comprising, in admixture:
>
> (a) a first active ingredient which is formoterol, a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt; and
>
> (b) a second active ingredient which is budesonide; and
>
> (ii) providing a recommendation to the patient to inhale the composition from the inhaler on an as-needed basis, as determined by the patient based on the patient's

symptoms, as a treatment and a preventive measure, when the patient experiences an increase in asthma symptoms.

The claim now has two parts: **"(i) providing an inhaler..."** and **"(ii) providing a recommendation to the patient to inhale the composition from the inhaler on an as-needed basis, as determined by the patient based on the patient's symptoms..."**.

While the term "**providing an inhaler**" does not find literal basis in the specification as filed, the reader of ordinary skill would certainly have understood that Appellant possessed this aspect of the invention. By describing several examples in which a Turbuhaler® dry powder inhaler containing the two active ingredients was prepared (see Examples 1-4 on pages 7-8), and also stating at page 6, lines 19-21, that "The ingredients of the system are preferably adapted to be administered from a dry powder inhaler, a pressurized metered dose inhaler, or a nebulizer," Appellant communicated to the reader of ordinary skill that Appellant possessed the concept of providing an inhaler to the patient, the inhaler containing a composition comprising the two specified active ingredients. Accordingly, step (i) of claim 13 as amended (and the identical step in each of the other independent claims, as amended) meets the written description requirement. Acknowledgement of this point is respectfully requested.

Step (ii) of claim 13 as amended begins "**providing a recommendation to the patient to inhale the composition from the inhaler on an as-needed basis...**". The term "**on an as-needed basis**" is literally recited in the specification at page 4, line 22. It finds further conceptual support throughout the specification, e.g., at page 2, line 23; page 3, lines 23 and 30; page 4, line 5; in the entire paragraph at page 4, lines 7-23; and in hypothetical Examples 5 and 6. Indeed, the Examiner acknowledged at page 4 of the Office action that the specification discloses administration of the composition "as needed." Acknowledgement of this point is respectfully requested.

The treatment that is to be carried out on an "as-needed" (or, to use the physician's term, "Pro Re Nata") basis is, of course, inhalation of the specified composition from an inhaler. This concept is supported throughout the specification. See, e.g., page 3, lines 21-27; and page 6, line 19, to page 7, line 4. Furthermore, one of ordinary skill would understand that any drug to

be self-administered by the patient has to come with recommendations for use (how much, when, and under what circumstances it should be administered). See the discussion of the "recommended dose regimen" at page 4, lines 1-5, and the descriptions of two different recommended dose regimens in Examples 5 and 6. Both of the recommended dose regimens in these two Examples include a recommendation that the patient use the composition "as needed," up to a recommended maximum daily dose; in Example 5, the patient also is told to take the combination as a regular maintenance treatment (in addition to rescue or as needed use) up to that recommended maximum daily dose. These two regimens are consistent with the recommended treatments disclosed throughout the specification, e.g., at page 4, lines 7-23. Accordingly, one of ordinary skill in the art of treating asthma patients would understand that Appellants possessed the concept of "**providing a recommendation to the patient to inhale the composition from the inhaler on an as-needed basis**..." as recited in amended claim 13. The same terminology now appears in claims 35, 36, and 43, replacing the "patient is instructed to inhale the composition on demand" language to which the Examiner newly objects. Claim 42 is slightly different in that it now recites "**providing a recommendation to the patient to take a maintenance dose of the composition, and, if the patient experiences acute asthma symptoms, inhale additional doses as needed to provide symptomatic relief.**" For support for that claim 42 language, see, e.g., page 2, lines 18-28, and Example 5. The points made above regarding the claim 13 amendments apply equally to claims 35, 36, 42, and 43. Acknowledgement that step (ii) of each of the independent claims meets the written description requirement is respectfully requested.

Appellant believes that the Examiner's concerns regarding written description of the appealed claims are unwarranted (particularly since the same concerns were presumably resolved to the Examiner's satisfaction five years ago), but nevertheless have omitted the objected-to terms from the claims, substituting new terms that should be acceptable. If for any reason the Examiner is not satisfied with the claims as presently amended, she is asked to telephone the undersigned to discuss the issue in the spirit of the Board's request that Appellant "take an active role in clarifying the foregoing issues."

**35 USC § 101, statutory subject matter**

According to the Office action at page 5, claims 13-36, 38, 42 and 43 (i.e., all of the pending claims) are rejected under 35 USC § 101 on the ground that the claimed invention is directed to what the Examiner characterizes as non-statutory subject matter. However, the Office action explains the rationale for this rejection solely with respect to claim 13. According to the Office Action at pages 5-6:

> Claim 13 requires only one positive step-instructs a patient to inhale a composition on demand. It is noted that a process is an act or a series of acts, performed upon the subject matter to be transformed and reduced to a different state or thing.
>
> According to Applicants, this step of instructing a patient can be performed by any number of routes, including printed matter (e.g., a product insert accompanying an inhaler). Therefore, this claim **is directed to the manipulation of an abstract idea (e.g., the communication of a concept) without any requirement that a practical application actually be associated with this abstract idea.**
>
> Neither transformation nor reduction would result from the claimed invention because whether the patient actually performs the administration of the claimed composition is not an element of the claim. (see Oral Hearing Transcript 11:4-8). The actual "reduction" or "transformation" would only take place with an actual administration of the claimed combination. In this case, there is no reduction or transformation would take place with the claimed invention because the claims do not recite necessary step of a practical application associated with this abstracted idea. (Emphasis and informal English in the original.)

Given that the above explanation is expressly applied just to claim 13, it is unclear whether the Examiner actually intended the rejection under § 101 to apply to all pending claims, and if so, whether the rationale for the rejection stated with respect to claim 13 was intended to apply identically to all claims, despite the different limitations in different claims. Absent an explanation of how the rejection is being applied to claims other than claim 13 (if indeed it is), Appellant cannot fully respond. If the Examiner intends to maintain the rejection, she is asked to explain how the rejection applies to each claim that is rejected on this ground, and to do so in a new, non-final Office action that provides Appellant a full and fair opportunity to respond to the restated rejection.

Regardless of whether the rejection is intended to apply to all of the claims or solely to claim 13, Appellant traverses.

Appellant believes that the Office has misapprehended the law regarding statutory subject matter. One must, of course, begin with the statute itself, which defines patentable subject matter as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 USC § 101. The present claims are drawn to a method of prevention and treatment, which would fall into the "process" category of § 101 (see the definition of "process" in 35 USC § 100(b)). Despite the very broad language of the statute, the U.S. Supreme Court has established that there are limits on the scope of patentable subject matter, noting in *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980), that, though "Congress intended statutory subject matter to 'include anything under the sun that is made by man,'…"The laws of nature, physical phenomena, and abstract ideas have been held not patentable." (Emphasis added.)

MPEP §2106 IV. provides a useful summary of the procedure to be followed by the Office in determining whether a given claim is drawn to statutory subject matter. MPEP § 2606 IV.C.1. says that, after confirming that the claimed invention falls within one of the statutory categories (here, the "process" category), the Examiner should next determine whether one of the three "judicial exceptions" (laws of nature, physical phenomena, and abstract ideas) is applicable.

The Office does not assert that Appellant is attempting to patent one of the prohibited types of subject matter, i.e., a "law of nature," "physical phenomenon," nor even an "abstract idea." Rather, the Office action takes the position that claim 13 (at least prior to the present amendment) is directed to "the manipulation of an abstract idea" (emphasis added), as though that were relevant to the statutory subject matter question. Even if one were to accept that this is an accurate description of the claimed method, it does not support a rejection under § 101, because it recognizes that Appellant has not attempted to claim an "abstract idea" *per se*. Claiming a method of manipulating an abstract idea is not the same thing as claiming an abstract idea *per se*, and there is no prohibition in U.S. law to claiming a method of "manipulating" an abstract idea. Indeed, one could characterize any method of utilizing computer software as being a method of "manipulating" the abstract ideas that are embodied in the software. The Examiner

will surely agree that methods of using software are routinely patentable. Likewise, any chemical process could ultimately be characterized as "manipulating an abstract idea," with the "abstract idea" being the fundamental physical principle behind the chemical process, and the "manipulating" being the steps of the process that takes advantage of that principle. Consequently, even if some claimed method could be characterized as "manipulation of an abstract idea," if anything that label would seem to take it out of the list of three judicial exceptions and dictate a conclusion that the claim satisfies § 101.

Noting that a claim drawn to a "practical application" of one of the judicial exceptions may well be patentable, even though a claim drawn to the judicial exception is not, MPEP § 2606 IV.C. sets forth two tests that are helpful for making this determination:

> A claimed invention is directed to a practical application of a 35 U.S.C. 101 judicial exception when it:
> (A) "transforms" an article or physical object to a different state or thing; or
> (B) otherwise produces a useful, concrete and tangible result, based on the factors discussed below.

Thus, a claimed invention that is a "practical application" under either test (A) or test (B) would be considered statutory subject matter. These tests are elaborated in MPEP § 2606 IV.C.2 (1) and (2), as follows.

MPEP 2606 IV.C.2 (1) Transformation

The MPEP explains that, if a claim "provides a transformation or reduction of an article to a different state or thing," the claim "meets the statutory requirement of 35 U.S.C. 101."

According to the Office action,

> It is noted that a process is an act or a series of acts, performed upon the subject matter to be transformed and reduced to a different state or thing....Neither transformation nor reduction would result from the claimed invention because whether the patient actually performs the administration of the claimed composition is not an element of the claim.

The Office appears to have arbitrarily decided that only administration of the composition can qualify as a "practical application" that produces the requisite "transformation" or "reduction" of

something. In reviewing the cases that discuss the concept of "transformation or reduction" (e.g., *Gottschalk v. Benson*, 409 U.S. 63 (1972), *Diamond v. Diehr*, 450 U.S. 175 (1981)), Appellant can find nothing that would support such a sweeping conclusion. Appellant points out that the "transformation" the Examiner seeks could be simply the education of the patient, who is "transformed" from one who does not have the recommendation recited in each of the amended independent claims, to one who does have it. If, as the Examiner implies, a person can be "transformed or reduced to a different state" by the act of administering the composition, it is equally logical to conclude that the person can be "transformed or reduced to a different state" (i.e., a more informed state) when he or she receives the recommendation specified in each claim. The amended independent claims also require providing an inhaler to the patient, thereby "transforming" the patient into a patient who has an inhaler. If the Examiner disagrees with Appellant's reasoning, she is asked to explain why, and to cite the authority on which she relies to support her position.

MPEP 2606 IV.C.2 (2) Useful, Tangible, and Concrete Result

Even if a given claim does not meet the "transformation" test, MPEP 2606 points out that the claim can still qualify as being directed to a practical application if the invention produces a "useful, tangible, and concrete result" (citing *AT&T Corp. v. Excel Communications*, 172 F.3d 1352, 1358-59 (Fed. Cir. 1999)). In *AT&T*, the "useful, tangible, and concrete result" was inclusion of certain information in records of telephone calls. *Id* at 1358. In a second case, *State Street Bank & Trust Co. v. Signature Financial*, 149 F.3d 1368, 1373 (Fed. Cir. 1998), the court opined that "a final share price momentarily fixed for recording and reporting purposes" qualified as a useful, tangible, and concrete result. If results as ephemeral as these can qualify as "useful, concrete and tangible," then certainly the result of the presently claimed method (a patient who has been provided with an inhaler and a recommendation as to how to use it to treat asthma) qualifies as well.

Despite this guidance in the MPEP and in the caselaw, the Office attempts to craft a different standard from whole cloth. After pointing to the fact that Appellant has agreed that the step of instructing a patient "can be performed by any number of routes, including printed matter," the Office then inexplicably asserts, "Therefore, this claim is directed to the manipulation of an abstract idea (e.g. the communication of a concept) without any requirement that a practical application actually be associated with this abstract idea." Appellant does not understand the logic behind this assertion. The "practical application" of the claim 13 method considered by the Examiner (i.e., prior to the present amendment) is quite apparent from the wording of the claim: the patient is instructed. A similar argument applies to the claim as presently amended: the patient is provided with an inhaler and a recommendation as to how to use it. It is unclear whether the Examiner is saying that no communication of a concept can ever constitute a "practical application" (an assertion that makes no sense, as there is no question that communicating an instruction regarding how to use a pharmaceutical agent to treat a condition is useful and "practical"), or if she is saying that it isn't a "practical application" simply because a particular route of communication is not specified in the claim. If the latter, Appellant would like to understand just why the Examiner believes the fact that the instruction can occur by any number of routes somehow detracts from the practicality of the result. The result is equally beneficial regardless of how the instruction is communicated. Clarification is requested.

In view of the above, Appellant asserts that claim 13, both prior to and post amendment, amply satisfies the criteria of § 101. If the Office intends to apply a similar rejection to the remaining claims, Appellant would appreciate an opportunity to respond to it once it is made explicit. Furthermore, as elaborated below, Appellant notes that the newly added claims 44-53 contain limitations that are pertinent to the grounds of rejection under § 101 as stated in the Office action, and need to be addressed separately.

New claim 44 depends from claim 13, adding the limitation "wherein step (i) comprises filling the inhaler's storage compartment with the composition." Thus, a physical object (the inhaler) is unequivocally "transformed to a different state" by the claimed method. To the extent such a physical transformation is necessary in order to satisfy § 101 (though Appellant maintains

it is not), claim 44 satisfies the requirement. New claims 45-47 are similar to claim 44, but depend from independent claims 35, 36, 42, and 43, respectively.

New claim 49 depends from independent claim 13 and specifies "wherein the recommendation causes the patient to inhale the composition on at least one occasion at a time the patient experiences an increase in asthma symptoms." The Examiner based the § 101 rejection of claim 13 on the fact that "whether the patient actually performs the administration of the claimed composition is not an element of the claim." Since claim 49 does require that the patient have inhaled the composition, it would appear that claim 49 should pass muster even under the Examiner's unusual standard. New claims 50-53 depend from independent claims 35, 36, 42 and 43, respectively, and add limitations similar (though not identical) to that of claim 49.

Recognition that all of the pending claims are drawn to statutory subject matter under § 101 is respectfully requested. For the record, Appellant notes that claims very similar to the present claims are routinely granted by the US Patent and Trademark Office. See, for example, the claims of U.S. Patent Nos. 7,122,566 and 6,683,102. In view of the similarity of those issued claims to the present ones, the current rejection for lack of statutory subject matter appears to be an arbitrary and capricious decision that is prohibited under the U.S. Administrative Procedure Act.

**35 USC § 103(a), obviousness**

Claims 13-15, 17, 18, 20-36, 38, 42, and 43 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Carling *et al.* (WO 93/11773, "New Combination of Formoterol and Budesonide"). Appellant traverses.

As the U.S. Supreme Court explained in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), and reiterated in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), analysis of obviousness under § 103(a) requires determination of the scope and content of the prior art, differences between the prior art and the claims in issue, and the level of ordinary skill in the pertinent art. *See also* the Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v.*

*Teleflex Inc.*, 72 Fed. Reg. 57526 (October 10, 2007). When applying § 103(a), the examiner must consider the claimed invention as a whole; must consider the cited reference(s) as a whole; and must view the reference(s) without the benefit of impermissible hindsight vision afforded by the claimed invention. MPEP 2141(II). Any rejection of a claim for obviousness must establish that one of ordinary skill in the art would have had a reason to alter the teachings of the art, in order to arrive at the claimed invention. *KSR*, 127 S. Ct. at 1741; *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In addition, the examiner's *prima facie* case must include a finding that one of ordinary skill in the art at the time the invention was made would have reasonably expected the claimed invention to work. *See*, *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). Such objective considerations as surprising results (*In re Soni*, 54 F.3d 746, 34 USPQ2d 1684 (Fed. Cir. 1995)), long felt but unsolved need (*Dow Chem. Co. v. American Cyanamid Co.*, 816 F.2d 617, 622, 2 USPQ2d 1350, 1355 (Fed. Cir. 1987), and skepticism of experts (*United States v. Adams*, 383 U.S. 39, 148 USPQ 479 (1966)) are also relevant to the obviousness inquiry.

All of the present claims except claim 43 and its dependents are drawn to methods of prevention and treatment of a patient's asthma symptoms, which methods comprise (i) providing an inhaler containing a composition comprising formoterol (or a pharmaceutically acceptable salt or solvate thereof or a solvate of such a salt) and budesonide, and (ii) providing a recommendation to the patient to inhale the composition from the inhaler. These claims differ in the details of the recommendation provided to the patient, as follows. Independent claim 13 requires that the recommendation be to inhale the composition **on an as-needed basis, as determined by the patient** based on the patient's symptoms, as a treatment and a preventive measure, when the patient experiences an increase in asthma symptoms. Independent claim 35 requires that the recommendation be to inhale the composition **on an as-needed basis, as determined by the patient** based on the patient's symptoms, as a complement to maintenance treatment of patient's asthma. Independent claim 36 requires that the recommendation be to inhale the composition **on an as-needed basis, as determined by the patient,** when the patient is expecting to encounter an asthma triggering event, as a preventative measure. Independent

claim 42 requires that the recommendation be to inhale a maintenance dose of the composition from the inhaler and, if the patient experiences acute asthma symptoms, to inhale additional doses **as needed for symptomatic relief**. And finally, independent claim 43 is drawn to a method of "reducing the incidence of acute asthma attacks in a patient" by providing the inhaler and a recommendation to the patient to inhale the composition from the inhaler **on an as-needed basis, as determined by the patient** based on the patient's symptoms, as a treatment and to reduce the incidence of acute asthma attacks, when the patient experiences an increase in asthma symptoms.

It can be seen from the above that each of the claims is limited to a method in which the patient is instructed to inhale the formoterol/budesonide composition either "**on an as-needed basis, as determined by the patient**" or "**as needed for symptomatic relief**". Arriving at these methods required an insight by Appellant: that leaving to the patient's discretion the question of how many doses of a combination budesonide/formoterol composition to take on any give day, according to the patient's determination of need, would greatly improve control over the patient's asthma and reduce the number of asthma attacks suffered by the patient; and that this could be done without incurring in practice a substantial risk of overdose of budesonide, a potent glucocorticosteroid. This insight was nowhere in the prior art, and in fact represented a radical departure from how patients were instructed to take budesonide-containing compositions prior to 1998, the priority date of the present application.

Carling *et al.*, WO 93/11773, is cited as rendering the claimed methods obvious. Carling *et al.* discloses treatment of asthma by inhalation of a combination of formoterol and budesonide from a single inhaler. According to Carling *et al.* at page 4, lines 19-21, "The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma." (Emphasis added.) Similarly, page 6, lines 22-29, says, "The intended dose regimen is a twice daily administration...." Such a set, twice-daily regimen has long been, and still is today, a standard asthma treatment protocol for anti-inflammatory glucocorticosteroids such as budesonide. Commonly termed "maintenance therapy," it is intended to reduce over the long term the chronic inflammation that, if

uncontrolled, can contribute to spasms of bronchoconstriction—*i.e.,* acute asthma attacks. Typically the asthma patient will also be prescribed an inhaler containing a short-acting bronchodilator for use as needed to stop an imminent or ongoing attack that occurs despite the glucocorticosteroid maintenance therapy regimen. Use of that short-acting bronchodilator is left to the discretion of the patient. In contrast, use of budesonide or other powerful glucocorticosteroids is not—or at least wasn't until the present invention. As will be clear from evidence discussed in detail below, prior art patients who were prescribed a budesonide-containing inhaler were warned not to take any more (or any fewer) doses from their budesonide inhaler than the two fixed doses per day prescribed by the physician for maintenance therapy. This reflects both what was perceived to be the relatively slow-acting nature of glucocorticosteroids, rendering them mostly useless in an acute attack, and the danger of systemic side effects from overdosing on glucocorticosteroids in general. While the physician had the discretion to adjust the size of the two fixed daily doses of glucocorticosteroid according to factors such as the age and weight of the patient or the severity of the patient's illness, such adjustments were solely at the discretion of the physician. The patient would not make that decision, and the number of administrations of budesonide or other glucocorticosteroid would generally remain at twice per day even if the prescribed fixed dosage per administration were changed by the physician. Evidence supporting these assertions, including statements derived from various inhaler product inserts, is already of record and is discussed below.

The Office Action cites Carling *et al.* for its teaching that a composition comprising both formoterol and budesonide can be used to treat asthma, noting at page 7 that Carling *et al.* "exemplify amounts of active agents per dose of inhalation, which calculate up to 8 inhalation per day without going over the maximum daily dosage" (non-standard English in the original). As best as Appellant can decipher it, the "up to 8 inhalation per day" is a reference to some of Carling *et al.*'s examples of inhalers described on pages 7-9 as delivering 12 μg of formoterol and either 100 or 200 μg budesonide, combined with Carling *et al.*'s teaching on page 6, lines 24-26, that a "suitable daily dose" of formoterol is 6 to 100 μg and a "suitable daily dose" of budesonide is 50 to 4800 μg. Thus, in theory one could inhale eight "puffs" from an inhaler

that delivers a combination of 12 μg formoterol and 100 or 200 μg budesonide per puff without exceeding what Carling *et al.* teaches is the upper end of the range of a suitable daily dose of formoterol (100 μg) and the upper end of the range of a suitable daily dose of budesonide (4800 μg). The reference itself actually says nothing about the number of inhalations per administration, rather only that those inhalations should be grouped into just two administrations per day ("the intended dose regimen is a twice daily administration" (page 6, lines 22-23)) and should deliver a total daily dose within the recommended ranges. Each of the two administrations per day intended by Carling *et al.* could, in theory, involve a single "puff" from an inhaler, or two or more "puffs"—whatever is needed to achieve the fixed daily dosage prescribed by the physician using whatever inhaler is commercially available. The mere fact that a particular inhaler delivers an amount per puff that is less than half of a prescribed daily dose does not mean that the prescribed daily dose should be spread out into more than two administrations per day, in contravention of Carling *et al.*'s explicit teachings that the intended dose regimen is twice daily. The Examiner's interpretation to the contrary, which is central to her obviousness theory, is therefore without basis in the reference.

The Examiner recognizes that Carling *et al.* does not teach that the patient should be instructed to inhale the composition on an "on demand" or "as needed" basis, as required by the claims. (Carling's reference to a "rescue medicine" at page 4, line 8, merely points out a benefit of inhaling the bronchodilator formoterol mixed with budesonide, as part of the maintenance therapy with budesonide in the fixed twice per day dosing regimen, as specified at page 4, lines 19-21.) As acknowledged in the Office Action at pages 7-8,

> The difference between Carling *et al.* and Applicant's invention is instructing a patient to inhale, on demand, as determined by the patient based on the patient's symptoms...[and] instructing patient to inhale additional doses as needed if he experiences asthma including acute asthmatic episode...(non-standard English in the original)

Though acknowledging this "difference," the Examiner concludes that despite this lack of explicit teaching in the reference, the instruction required by the claims would have been obvious in view of Carling *et al.*'s teachings:

> However, to instruct the patient to inhale, on demand, as determined by the patient's symptoms in acute asthmatic episode is obvious since Carling et al. teach that the dosages strongly depends on the severity of disease (mild, moderate, severe asthma) and the suitable daily dosage is up to 8 inhalation. Office Action at page 7.

In order to arrive at this conclusion, the Examiner had to make two assumptions about the Carling *et al.* reference: *first*, that Carling *et al.* can be read as teaching that the maximum daily dose of the active ingredients can be spread out in more than two, and as many as eight, discrete administrations over the course of the day, and *second*, that Carling *et al.* suggest that it is up to the patient to determine how many of those eight administrations to take on any given day, based on "severity of disease". The lack of basis for the *first* assumption is discussed above. The *second* assumption is even more far-fetched than the first. It seems to derive from the sentence at page 6, lines 27, of Carling *et al.* that "[the] particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)." This sentence of course was intended to mean that the physician will determine a fixed dose that depends on the patient's age, weight, and severity of disease, and not that the physician should instruct the patient to make these determinations for himself or herself. In fact, it seems fairly ridiculous to have to explain that point at all. The twice-daily dose regimen called for by Carling *et al.* is a fixed dosage prescribed by the physician for the patient to inhale two times per day, every day, no more and no less, consistent with what was known in the art about administration of any budesonide-containing composition for treatment or prevention of asthma symptoms. The amount inhaled at each administration can be varied only by a change in the prescription by the physician, again consistent with what was known in the art about administration of any budesonide-containing composition in the asthma context. This is not "on an as-needed basis, as determined by the patient based on the patient's symptoms." It is *fixed.*

As evidence that one of ordinary skill in the art of asthma therapy would have agreed with Appellant's interpretation of Carling *et al.*, Appellant refers to certain exhibits submitted with the Amendment dated June 29, 2005, and again as Exhibits A-F in Appellant's Appeal Brief submitted March 3, 2006. (Rather than clutter the file with yet another copy, Appellant will

simply refer hereinafter to the exhibits in the Appeal Brief.) The exhibits show that from a date prior to the present priority date to as late as 2003, glucocorticosteroid-containing therapeutics were routinely prescribed for fixed-dosage use twice per day as maintenance therapy, with the patient forbidden to vary daily dosage outside that regimen, whether "on demand," "as needed", or for any other reason. Once one understands how inhaled glucocorticosteroids such as budesonide were typically prescribed for asthma patients prior to Appellant's invention, it is apparent that Appellant's (and not the Examiner's) interpretation of Carling *et al.* is the one that a person of ordinary skill would have taken from this reference.

Certain sections of these Exhibits have been circled and labeled in the margin with a capital letter for ready reference.

The glucocorticosteroid budesonide is the sole active ingredient in an inhaler sold under the trademark Pulmicort® Turbuhaler® for maintenance treatment of asthma. A copy of a 1997 product insert packaged with the Pulmicort® Turbuhaler® product was submitted as Appeal Brief Exhibit A. Recommended starting doses and highest recommended doses for various categories of patients are set out in a table in this document (Exhibit A, page 4, section A); each and every one of these doses is to be administered "twice daily." There is no provision for additional doses to be taken "as needed." Indeed, the section titled "Patient's Instructions for Use" on page 2 of the document (see entire bottom half of page 2) repeatedly and emphatically instructs the patient not to take more or less than the exact dose prescribed by the physician, regardless of whether the patient is feeling better or worse on a given day.

The patient instructions concerning dosage (labeled as section B on page 2 of Exhibit A) are quoted in their entirety below:

DOSAGE

- Use as directed by your doctor.
- It is **VERY IMPORTANT** that you follow your doctor's instructions as to how many inhalations to take and how often to use your Pulmicort Turbuhaler
- **DO NOT** inhale more doses or use your Pulmicort Turbuhaler more often than your doctor advises.
- It may take 1 to 2 weeks or longer before you feel maximum improvement so **IT IS VERY IMPORTANT THAT YOU USE PULMICORT TURBUHALER REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR**

**DOSE EVEN IF YOU ARE FEELING BETTER**, unless told to do so by your doctor.

- If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose. (Emphasis in original).

These instructions provide objective evidence that the paradigm for treatment of asthma with budesonide in 1997 was for a physician to prescribe a particular number of doses (generally two) per day for a patient and instruct the patient to take exactly that number of doses, no more or less. The third and last bullet points of the above instructions are particularly telling. Under no circumstances was the patient to take more doses than the specific number prescribed by the physician. Even if the patient missed a dose, the patient was not to take even a single extra dose. This is directly contrary to the Examiner's assertion that

> The skilled artisan would have been motivated to instruct the patient to use Carling's composition as needed bases up to 8 inhalations a day with reasonable expectation of successfully achieving maximum benefit in treatment of any severity condition of asthma in general including acute asthmatic condition. (Office Action at pages 8-9; non-standard English in the original.)

Exhibit A also says:

> Patients should take the medication as directed and use PULMICORT TURBUHALER at regular intervals twice daily since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician....If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician. (Exhibit A, page 3, section C.)

This further illustrates that the physician, and not the patient, determines when the dosage of budesonide can be altered for a given patient. If the patient suffers an exacerbation of symptoms, he must turn to a different type of medication (a short-acting bronchodilator) for immediate relief:

**"PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma."** Exhibit A, page 2, section D.

**"PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required."** Exhibit A, page 1, section E.

**"If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur."** Exhibit A, page 3, section F.

**"Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA [hypothalamic-pituitary-adrenal] dysfunction [a deleterious side-effect of glucocorticosteroid overdosing] may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose."** Exhibit A, page 3, section G.

These warnings make it clear that budesonide was understood to be useful for long-term prevention of asthma symptoms when used regularly in a fixed dose that is set (and carefully monitored) by the physician according to the patient's needs, but had no role in short-term relief of acute symptoms. The only medication that could be taken by the patient on an as-needed basis was a short-acting bronchodilator. The physician was explicitly directed to ensure that the patient received the lowest effective fixed dose of budesonide. Even in 1997 (four years after Carling *et al.*), instructing the asthmatic patient to take additional doses of a budesonide composition on an as-needed basis, *i.e.,* at the patient's own discretion, was strictly forbidden. There was no evidence that taking budesonide more frequently or in larger doses than prescribed would be of any benefit to the patient, and there was a significant risk of harm.

That 1997 product insert pertains to budesonide alone, rather than a combination product. There are now at least two combination glucocorticosteroid/bronchodilator inhalation products (comparable to the combination product disclosed by Carling *et al.*) on the market for treatment of asthma. Product inserts for the two marketed products were submitted with the Appeal Brief

as Exhibits B and C. As elaborated below for both products, the physician instructs the patient to inhale a set dose, twice per day--consistent with Appellant's (and not the Examiner's) interpretation of Carling *et al.*

The first combination product is SYMBICORT TURBUHALER, a budesonide/formoterol inhalation powder product similar to that disclosed by Carling *et al.* Exhibit B is a product insert circa 2001 for that product. It says that the **"recommended dosage"** is 1-2 inhalations twice daily (Exhibit B, page 1, section A); when control of symptoms is achieved with the twice daily regimen, the physician can choose to reduce the number of inhalations to one daily (Exhibit B, page 1, section B).

The insert instructs the physician to adjust the dosage to reflect the severity of the particular patient's disease: **"The dosage of the components of Symbicort Turbuhaler is individual and should be adjusted to the severity of the disease. This should be considered when treatment with combination products is initiated."** Exhibit B, page 1, section C.

There is nothing in the document recommending that the patient inhale the product "as needed." To the contrary, use outside of the fixed dose is dangerous and forbidden: **"If patients find the treatment ineffective, or exceed the current dose of the fixed combination, medical attention must be sought."** Exhibit B, page 2, section D.

Moreover, **"increasing use of rescue bronchodilators [that is, a quick-acting bronchodilator such as indicates a worsening of the underlying condition and warrants a reassessment of the asthma therapy"; "patients should be regularly reassessed by a doctor, so that the dosage of Symbicort Turbuhaler remains optimal. The dose should be titrated to the lowest dose at which effective control of symptoms is maintained."** Exhibit B, page 2, section E; and page 1, section F, respectively (emphasis added).

These instructions clearly indicate that if the patient experiences an increase or decrease in symptoms, the patient is to notify the physician so that the treatment protocol can be reassessed (and if necessary, adjusted) by the physician. Adjusting the dosage from day to day at the patient's discretion is nowhere contemplated.

As further evidence that the Symbicort Turbohaler® product (spelled "Turbohaler" in the United Kingdom)was known to be used only once or twice per day, as explicitly instructed by the patient's physician, and never more, Appellant directs the Examiner's attention to item AA on the Form PTO-1449 enclosed in the Information Disclosure Statement submitted herewith. Item AA is a patient instruction leaflet provided to patients with their Symbicort Turbohaler® in the United Kingdom circa 2001 (see the date in the lower left corner of the last page), well after the present application's priority date. See in particular the information about "Dosage" on the second page, first column: Your doctor will advise you of the correct dose to treat your asthma…The doctor will reduce your dose to the lowest dose needed to control your asthma. **Do not use Symbicort to relieve an acute attack, for this you should use your blue 'relief' inhaler.**" (emphasis added) (The "blue 'relief' inhaler" is a separate inhaler containing a quick-acting bronchodilator and no steroids, and is reserved for use when the patient experiences asthma symptoms, not for maintenance purposes.)

The second combination product is the Advair Diskus® fluticasone propionate/salmeterol xinafoate inhalation powder product. This combination is prescribed for use twice per day, at a dose set by the physician. (Like budesonide, fluticasone propionate is a glucocorticosteroid, and like formoterol, salmeterol xinafoate is a beta-2 agonist.) The Patient's Instructions for Use (March 2003) for this product, attached to the Appeal Brief as Exhibit C, emphasizes repeatedly that the product must be used neither more nor less often than instructed by the physician. The pertinent portion of these instructions, found on page 2 of the insert, is reproduced below:

2. It is important that you inhale each dose as your doctor has advised. The label will usually tell you what dose to take and how often. If it doesn't, or if you are not sure, ask your doctor or pharmacist. **Do not use ADVAIR DISKUS more frequently than 2 times daily, morning and evening, approximately 12 hours apart, at the recommended dose of 1 inhalation each time.**
3. ADVAIR DISKUS delivers your dose of medicine as a very fine powder **that most, but not all, patients can taste or feel.** Whether or not you are able to taste or feel your dose of medicine, you should not exceed the recommended dose of 1 inhalation each morning and evening, approximately 12 hours apart. If you are not sure you are receiving your dose of ADVAIR DISKUS, contact your doctor or pharmacist.
4. You may feel better after the first dose of ADVAIR DISKUS; however, it may take 1 week or longer to achieve maximum benefit. It is **IMPORTANT THAT YOU USE ADVAIR DISKUS REGULARLY. DO NOT STOP TREATMENT EVEN IF YOU ARE FEELING BETTER** unless told to do so by your doctor.
5. If you miss a dose, just take your next scheduled dose when it is due. **DO NOT DOUBLE** the dose.
6. **DO NOT USE ADVAIR DISKUS TO *RELIEVE* SUDDEN ASTHMA SYMPTOMS** (e.g., sudden severe onset or worsening of wheezing, cough, chest tightness, and/or shortness of breath that has been diagnosed by your doctor as due to asthma). **An inhaled, short-acting bronchodilator such as albuterol should be used to *relieve* sudden asthma symptoms.** If you do not have an inhaled, short-acting bronchodilator, contact your doctor to have one prescribed for you. **You should continue to take ADVAIR DISKUS as instructed by your doctor.**

The patient is adamantly instructed not to use the combination therapy more frequently than 2 times daily, spaced approximately 12 hours apart, and is told to inhale only the recommended dose of 1 inhalation each time. The patient is further instructed not to use the product to relieve sudden asthma symptoms. Like the evidence discussed above, this evidence (from 2003) is directly contrary to the Examiner's assertions regarding what would have been "obvious" to one of ordinary skill in the art ten years earlier, in view of Carling *et al.* in 1993.

Clearly even as late as 2003 (long after the 1998 priority date of the present application), glucocorticosteroid-containing inhaled therapeutics were routinely prescribed solely for fixed-dosage use as maintenance therapy, and not for immediate relief of worsening symptoms. One of ordinary skill in the art of inhaled glucocorticosteroid therapy for treatment of asthma would have understood in 1998 that patients were never instructed to take inhaled glucocorticosteroids on an "as-needed basis." Carling *et al.* would certainly not have been read as recommending such a radical—and potentially dangerous—departure from the norm.

Further evidence concerning the proper interpretation of Carling *et al.* is provided by the publications submitted with the Appeal Brief as Exhibits D and E. Exhibit D is a journal article (O'Byrne *et al.*, "Budesonide/Formoterol Combination Therapy as Both Maintenance and Reliever Medication in Asthma," *Am J Respir Crit Care Med* 171:129-136, 2005) discussing the positive results of a recent clinical trial studying the efficacy of Appellant's claimed method for reducing the incidence of asthma exacerbations and other asthma symptoms. Exhibit E (Barnes, "A Single Inhaler for Asthma?" *Am J Respir Crit Care Med* 171:95-96, 2005) is an editorial in the same journal issue. Dr. Barnes states his opinion that "the study by O'Byrne and his colleagues may lead to changes in the paradigm of asthma management...." Exhibit E, page 95, last paragraph, emphasis added. Moreover, Dr. Barnes views the success of Appellant's treatment protocol as "remarkable", even several years after Appellant's priority date:

> The remarkable, and somewhat unexpected, finding was that the treatment with combination inhaler for both maintenance and relief markedly reduced the number of severe exacerbations (the primary outcome measure) over the 1-year treatment period compared with other treatments, but also reduced the need for oral corticosteroids, improved symptom control, and lung function compared with the other treatment regimens. (page 95, col.1, last paragraph)

Dr. Barnes explains in the carryover sentence of col.1-2 one reason why this approach was not previously contemplated: "A concern about this approach is that some patients might end up using the combination inhaler frequently and therefore receive an unacceptably high dose of inhaled corticosteroid." He then notes that this turned out not to be a problem in practice. In fact, the patients instructed to take the budesonide/formoterol combination on an as-needed basis inhaled on average only one additional dose per day, yet this approach was more effective in preventing exacerbations than doubling the fixed daily amount of budesonide had proven in a different study. Dr. Barnes notes that these are "surprisingly good results" (page 95, col.2, first full paragraph).

It is to be kept in mind that these statements by Dr. Barnes, including the characterization of the O'Byrne *et al.* report as including "surprisingly good results," were made in 2005, twelve years after the Carling *et al.* reference was published. In the heavily researched field of asthma treatment, if Appellant's invention had indeed been obvious from Carling *et al.*'s teachings, it

would not, twelve years later, have been regarded as the radical departure from the norm implied by the Barnes editorial. As the Federal Circuit stated in *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 698 (Fed. Cir. 1998), "Expressions of disbelief by experts constitute strong evidence of nonobviousness." See also MPEP 716.05. Barnes' objective characterization of Appellant's treatment as "remarkable" and the results as "surprisingly good" certainly qualifies as strong evidence of nonobviousness.

The Supreme Court in *Graham* explained that, to reach a proper determination under 35 U.S.C. § 103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the Appellant's invention was unknown and just before it was made. "The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry." *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991). In view of all factual information, the Examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. MPEP 2141.

The exhibits discussed here (particularly Exhibit A) help to establish the level of ordinary skill in the art at the time of Carling *et al.* and at the filing date of Appellant's application. With this level of ordinary skill in the art in mind, Appellant turns to the question of whether the Examiner has met her burden of establishing (1) that one of ordinary skill in the art would have had a reason to arrive at the presently claimed methods (*KSR* , 127 S. Ct. at 1741; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)); and (2) that one of ordinary skill in the art would have reasonably expected the claimed invention to work (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)), both being essential elements of any *prima facie* case of obviousness. These elements are addressed in turn.

***Reason (motivation):*** The Examiner's position regarding motivation is set forth at page 8 of the Office Action. Appellant understands the Examiner's position to stem from a combination of certain interpretations of Carling *et al.*, which Appellant restates as follows:

(a) the Examiner's deduction that the maximum dosage recommended by Carling *et al.* at page 6, lines 24-27, can be divided into eight separate inhalations;

(b) the Examiner's conclusion that, because the eight inhalations add up to no more than Carling *et al.*'s maximum suggested daily dose, all eight could be "safely inhaled" by a patient on any given day, at the patient's discretion; and

(c) the Examiner's view that Carling *et al.*'s statement on page 6, lines 27-29, that "[the] particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)" means that the patient should be instructed to make the determination of his/her dosage on any given day, up to a total of eight inhalations.

Appellant believes these interpretations of Carling *et al.*'s teachings are not accurate representations of how one of ordinary skill in the art of asthma treatment would have read this reference. For example, the Examiner has made the breathtakingly unwarranted assumption (paraphrased in part (b) above) that every asthma patient will be able to "safely inhale" even the high end of the ranges of "suitable daily doses" set forth at page 6, lines 24-27, of Carling *et al.* (the ranges being 6-100 μg of formoterol and 50-4800 μg of budesonide). Even if Carling *et al.* hadn't gone on to explain that the "particular dose" depends "strongly" on patient-specific factors ("the particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc)," one of ordinary skill in the art of asthma treatment would clearly not have read Carling *et al.*'s teachings about dosage ranges as meaning <u>all</u> patients can safely inhale <u>all</u> doses up to and including the maximum. That simply is not reasonable. Young children, for example, or very small adults, would not be able to safely inhale as high of a daily dosage as could be handled by a 200 lb. adult. Further, the Examiner's assumption is inconsistent with the knowledge in the art that budesonide and other glucocorticosteroids are potent drugs with dangerous side effects, whose use must be carefully monitored in every patient to avoid overdosing (see evidence to that effect discussed above).

Appellant has previously explained why the Examiner's interpretation of Carling *et al.*'s statement quoted in part (c) above is far off base. Carling *et al.*'s reference to "severity of the disease" as being one of the bases for setting the amount of the twice-daily dose of the composition does <u>not</u> mean that the patient should be told to take more doses if his/her disease is particularly severe on a given day. It simply means that the overall level of the patient's disease

is one of the factors (along with the patient's age, weight, etc.) the prescribing physician should take into account in setting the twice-daily dose. Thus, this statement cannot be read as providing any motivation to instruct the patient to inhale the composition "as needed," as required by the present claims. Without a motivation to alter Carling *et al.*'s teachings to arrive at the presently claimed methods, the obviousness rejection fails.

***Expectation of Success:*** The statement in the Office Action that seems to communicate the Examiner's view regarding "expectation of success" is at pages 8-9:

> The skilled artisan would have been motivated to instruct the patient to use Carling's composition as needed bases up to 8 inhalations a day with reasonable expectation of successfully achieving maximum benefit in treatment of any severity condition of asthma in general including acute asthmatic condition. (Non-standard English in original)

As Appellant understands it, the Examiner is saying that one of ordinary skill would have a reasonable expectation of successfully treating any and all asthma patients by simply handing them an inhaler containing Carling *et al.*'s formoterol /budesonide composition and telling them to inhale any amount per day that they wish, up to and including the maximum daily dose of 100 µg formoterol and 4800 µg budesonide, because that will give them "maximum benefit." Appellant points out that Carling et al. warns the reader that the particular dose of the combination "will strongly depend" on patient-specific factors, factors that are not normally left to the judgment of the patient. While Carling et al. was referring to a fixed, twice-daily dose (there being no allowance in Carling et al. for anything other than a fixed, twice-daily dose), the same would certainly be true of any additional doses taken each day. Further, at least with respect to the budesonide part of this composition, Appellant has provided ample evidence that one of ordinary skill in 1997 would NOT have had such a reasonable expectation of success under the scenario the Examiner believes is "obvious". In fact, the very idea would have shocked the medical establishment. (See above discussion of Exhibit A.) This view apparently had not changed by 2001 when the formoterol/budesonide combination product was marketed with a product insert warning the user not to exceed the fixed, twice-daily dosage prescribed by the physician. (See above discussion of Exhibit B and item AA of the enclosed Form PTO-1449.) Because the Examiner has not established that one of ordinary skill at the 1998 priority

date would have had a reasonable expectation that the claimed methods would succeed, her *prima facie* case of obviousness must fail.

> At the top of page 9, the Office action states a new argument:
>
> Further, patients disclosed by Carlings who is conventionally as taught by Carlings, e.g., two-times per day to prevent and treat asthma symptoms would be included in the range of "demand" because those patients may only "need" twice a day dosing per their medical condition. (*Informal English in the original.*)

Though this passage is not entirely clear, Appellant understands the Examiner to be admitting that Carling *et al.* teaches that the budesonide/formoterol combination should be administered just twice per day (a remarkable admission, in view of her other arguments to the contrary). The passage also appears to observe that it is possible a given patient taking the combination twice per day as taught by Carling et al. will not need more than those two administrations per day, so will be taking the combination in a manner that allegedly qualifies as "as needed" or "on demand." It is not apparent whether the Examiner meant this as further support for the obviousness rejection, or was postulating that the claims might be inherently anticipated by this hypothetical situation.

In response, Appellant point out that the number of times per day that the patient inhales a dose of the combination is not an element of any of the independent claims, nor is there any requirement in any claim except new claims 49-53 that the patient inhale any dose at all. Thus, whether or not one can categorize a given prior art patient's twice-daily dosing as having been on what was inherently an "as needed" basis is irrelevant to the patentability of the present claims. The relevant question with respect to claim 13 (as amended) is whether the prior art taught providing a recommendation to the patient to inhale the composition on an as-needed basis, as determined by the patient based on the patient's symptoms, when the patient experiences an increase in asthma symptoms. A recommendation to inhale the composition twice per day, every day, regardless of symptoms, is not the recommendation required by the claim, and a patient who receives a recommendation to inhale the composition exactly twice per day, no more and no less (as taught by Carling *et al.*), has not received a recommendation to inhale the composition in the manner specifically required by the claim. It is the substance of the recommendation, and not the

number of inhalations per day that result, that determines whether claim 13's step (ii) was ever carried out in the prior art. Furthermore, the Examiner has cited no evidence to indicate that any patient on Carling et al.'s rigid twice-daily regimen actually happened to experience "an increase in asthma symptoms" (see the last clause of claim 13) prior to, or at least in conjunction with, administering each of his twice daily inhalations. Thus, the Examiner's speculation is not pertinent to either obviousness or anticipation of claim 13. Similar reasoning applies to the rest of the claims.

The above evidence and arguments demonstrate that the Examiner has not met her burden in making out a *prima facie* case of obviousness. In addition, Appellant has already made of record in this case, including in the Appeal Brief, powerful objective evidence of nonobviousness to rebut the Examiner's case. Such objective evidence must be taken into account by the Examiner. *In re Soni*. Rather than repeat the evidence again here, Appellant urges the Examiner to review Appellant's Appeal Brief, particularly pages 27-29 and Exhibits D and E. This evidence makes it clear that one of ordinary skill in the art of asthma therapy at the priority date would not have interpreted Carling *et al.* as suggesting that patients should be instructed to inhale a budesonide-containing product "on an as-needed basis, as determined by the patient." The paradigm for use of budesonide-containing products dictated fixed dosage use for maintenance therapy, not potentially variable dosage as determined day-to-day by the patient for relief of an acute attack or when the patient expects to encounter an asthma-triggering event.

Because Carling *et al.* does not teach or suggest administration of a combination of budesonide and formoterol on an as-needed basis, as determined by the patient, as required by the claims, and one of ordinary skill in asthma therapy at the filing date of Appellant's application would not have read Carling *et al.* to describe such methods, the independent claims are not obvious in view of Carling *et al.*

Claims 14, 15, 17, 18, 20-34, and 38 depend from claim 13; they are therefore patentable over Carling *et al.* for at least the reasons discussed above.

Claims 16 and 19 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Carling *et al.* (as applied to claims 13-15, 17, 18, 20-36, 38, 42, and

43) and further in view of Aberg *et al.* (U.S. Patent 5,795,564) and Ryrfeldt *et al.* ("Pulmonary disposition of the potent glucocorticoid budesonide, evaluated in an isolated perfused rat lung model," *Biochem. Pharmacol.* 38:17-22, 1989, Abstract). Aberg *et al.* is cited for its alleged disclosure of the (R,R) isomer of formoterol (a limitation of claim 16), and Ryrfeldt *et al.* is cited for its alleged disclosure of the 22R epimer of budesonide (a limitation of claim 19). Neither reference makes up for the deficiencies of Carling *et al.* described in detail above. Nor does either reference contradict the surprising results and other indicia of nonobviousness discussed above. Thus, claims 16 and 19 are patentable over the cited references for at least the reasons set forth above.

In view of the foregoing, the rejection of claims 13-36, 38, 42, and 43 as obvious in view of Carling *et al.* is unwarranted, and should be withdrawn.

It is believed that all claims are in condition for allowance, and such action is requested. The fee in the amount of $1,050 for the three month extension of time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of a Deposit Account authorization. Apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 06275-188001 / D1576-1P US.

Respectfully submitted,

Date: June 3, 2008

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
USPTO Customer No. 26164
Telephone: (617) 542-5070
Facsimile: (877) 769-7945